

REMARKS:

New claim 26 has been added. Basis for the added claim may be found in original claim 1 and in the Summary in the specification, among other places.

Claims 12-25 have been withdrawn, and Applicants reserve these claims to be prosecuted in a later filed application.

Claims 1-5 and 8 were rejected under 35 USC §112 as being indefinite. The phrase “composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl of the second nucleoside” was rejected as “not adequately described by the claims”.

A claim complies with the second paragraph of Section 112 if one can ascertain from the claim what is covered by the claim and what is not covered by the claim. See, for example, *In re Goffe*, 188 USPQ 131 (CCPA 1975), where the CCPA stated:

To determine whether the claim language is definite we must examine the claims to see whether the metes and bounds of the present invention can be adequately determined from the claim language.
(Id. at 135.)

See also, *In re Gaubert*, 187 U.S.P.Q.664 (CCPA 1975), where the CCPA reversed a determination that a claim was vague and indefinite. The Court described the statutory purpose of the second paragraph of Section 112 relating to claims as follows:

Its purpose is to provide those who would endeavor, in the future enterprise, to approach the area circumscribed by the claims of a patent, with the adequate notice demanded by due process of law, so that they may more readily and accurately determine the boundaries of protection involved and evaluate the possibility of infringement and dominance.
(Id. at 667.)

In *In re Fuetterer*, 138 USPQ 217 (CCPA 1963), the CCPA reversed an appeals board decision upholding the rejection of claims directed to particular tire compositions. These compositions included “one or more inorganic salts which are effective in maintaining the carbohydrate, protein, or mixture thereof, in colloidal suspension”. (Id. at 219.) The record showed that, in making their decision, the appeals board stated that “since the alleged novelty appears to reside in the result desired to be obtained by the

salts, it is not proper to define the salt by what it is supposed to do rather than what it does." (Id. at 221.) In reversing the appeals board decision, the CCPA first noted that " 'functional' language in claims is not expressly condemned by the patent statutes." (Id.) The CCPA also stated:

It is true that appellant's inorganic salt is defined in terms of "what it does" rather than "what it is." We note, however, that the Supreme Court, in a seldom quoted passage in the Wabash case, stated, [citation omitted] "A limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable." Appellant in the instant case has made just such a use of terms of result to define an essential quality of his inorganic salts.

(Id. at 222.)

The present Applicants thus note that the courts have supported the use of functional statements in claims. Applicants further assert that the facts of the current case resemble the Fuetterer case and the analysis applied by the Fuetterer court should thus be analogous. The Fuetterer court proceeded to analyse the rejection:

The rejection of the claims for "undue breadth" places particular emphasis on (1) an alleged "undue burden upon the public *to determine* what salts are *suitable* for obtaining the desired results" [emphasis in the original], and (2) an alleged "undue [amount of] experimentation" required of those skilled in the art to determine those salts possessing the "function asserted" by the instant claims. The undue breadth rejection phase of the instant case appears in the following posture. Appellant has described his invention as comprehending the use therein of any inorganic salt capable of performing a specific function in a specific combination and he has disclosed specifically four such salts which are capable of performing this function. The examiner and the board, believing that not all inorganic salts are capable of performing this function and that one skilled in the art would not know offhand which inorganic salts are capable of so functioning, have rejected the claims as "unduly broad."

It is clear that the instant claims do not comprehend a class of inorganic salts of any greater breadth than is comprehended by the invention description. [fn deleted] It is equally clear from this description and appellant's brief that, in the words of the second paragraph of section 112, "applicant regards as his invention" the combination with his other tread ingredients of any inorganic salt capable of "maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension * * *." It is exactly this combination which appellant has particularly pointed out and distinctly claimed in compliance with the second paragraph of section 112. If,

therefore, as the examiner alleges, many an “inorganic salt * * * would not be operative for appellant's purpose,” this criticism bears only on the sufficiency of the invention description. But its adequacy under the first paragraph of section 112 has not been questioned.

We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of undisclosed salts to operate in appellant's claimed combination beside the point. Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure. The only “undue burden” which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant. The Patent Office would require him to do research on the “literally thousands” of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming colloid suspending agents but tire tread stock composed of a combination of rubber and other ingredients.

(Id. at 222-23.)

Now, applying the decision of *In re Fuetterer* to the facts of the current case:

The reasoning set forth in the office action for the rejection under §112 was that the “skilled artisan would not be fully apprised of the metes and bounds [sic] of the instant method, as applicant has failed to set forth the critical components of said composition which promotes the concurrent oxidation of the phosphate and the deprotection of the hydroxyl group.” Applicants assert, however, that the current specification teaches that “the oxidation of the backbone of the elongated chain and the deprotection of the reactive site in the elongated chain occur at substantially the same time upon application of a single *combined oxidation/ deprotection reagent composition* (emphasis added)”.

(Summary, 2d para.) Thus, just as the *Fuetterer* specification taught “one or more inorganic salts which are effective in maintaining” the indicated colloidal suspension, the current specification teaches application of a *combined oxidation/ deprotection reagent*

composition which is effective to concurrently oxidize the phosphite (formed in step (a)) to a phosphate and deprotect the protected hydroxyl of the second nucleoside.

Applicants note that the claims are NOT directed to the combined oxidation/ deprotection reagent composition per se; the claims are directed to, for example, the “method of synthesizing a polynucleotide, comprising (a) coupling a second nucleoside to a first nucleoside through a phosphite linkage, wherein the second nucleoside has a non-carbonate protecting group protecting a hydroxyl; and (b) exposing the product of step (a) to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl of the second nucleoside.

Thus, continuing with the analysis analogously to the Feutterer court, if others in the future discover combined oxidation/ deprotection reagents (other than those enumerated in the current specification) that do have such properties, it is clear Applicant will have no control over them per se, and equally clear that the current claims should not be so restricted that they can be avoided merely by using some combined oxidation/ deprotection reagents not specifically named by appellant in his disclosure.

Furthermore, and directly on point with the reasoning set forth in the office action for the rejection under §112 that “the skilled artisan would not be fully apprised of the metes and” bounds of the claims, Applicants assert that the skilled artisan would be readily able to determine whether the combined oxidation/ deprotection reagent composition has oxidized the phosphate group and deprotected the hydroxyl group. Given the disclosure of the specification, the skilled artisan would be able to determine the presence of the resultant phosphate group and deprotected hydroxyl group using only routine experimentation, thus readily determining whether the composition used by the skilled artisan in a method to synthesize a polynucleotide reads on the current claims.

Also on point with the reasoning set forth in the office action for the rejection under §112 that Applicants have “failed to set forth the critical components of said composition”, Applicants point to the current specification, which discusses combined

oxidation/ deprotection reagent compositions, e.g. at pages 22-26. Applicants thus disclose (1) an alpha effect nucleophile, such as (2) an inorganic peroxide, or (3) an inorganic peroxide having the formula $M+OOH^-$, (4) an organic peroxide, particularly (5) an organic peroxide having structure (V), (6) an organic peroxide having structure (VI), or (7) an organic peroxide having structure (VII), (8) oxaziridines, (9) iodine, etc. The Applicant could continue to list compounds disclosed in the specification (such as (10) $t\text{-BuOOH}$, and (11) $m\text{CPBA}$), as well as solvents (aqueous or non-aqueous) pH (acidic, neutral, basic), to show that sufficient teaching has been given in the specification. Applicants further note that the exact composition of the combined oxidation/ deprotection reagent composition may vary, as the specification teaches at page 23: "The reagent will thus be selected based upon choice of protecting group and reaction conditions desired based upon whether aqueous or non-aqueous conditions are desired, whether acid catalyzed depurination of the product is a concern, or other considerations as will be apparent to the skilled practitioner given the disclosure herein." The Applicants further note that it is not the function of the claims to explain details of the invention, which is the function of the specification. Applicants should not be required to add details to the claims where terms have been adequately described in the specification, as is the case here.

As compared to the specification in Feutterer (which showed only four embodiments of the inorganic salts) the above list of 11 descriptions pertaining to the combined oxidation/ deprotection reagent compositions, as well as the even further information of the specification (e.g. at pp. 22-26), leads to the conclusion that the present Applicants have sufficiently well described the methods of synthesizing polynucleotides set forth in the current claims. Again, following the analysis of the Feutterer court set out above, the Patent Office should not require the Applicants to do research on the many possible combined oxidation/ deprotection reagent compositions "and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming" combined oxidation/ deprotection reagent compositions per se, but a method of synthesizing polynucleotides.

Thus, the analysis of the Feutterer court applies analogously in the present case. The claims, read in light of the specification, particularly point out and distinctly claim the subject matter of the invention as required under section §112.

THE ART REJECTIONS

Claims 1-11 were rejected under USC §103(a) as being unpatentable over the combination of Dellinger '030, Crameri '246, and Manoharan '819.

The office action summarizes the inquiries for determining obviousness under §103(a), as set forth in *Graham v. Deere*. The office action then describes claim 1 of the present application and describes the Dellinger '030 patent, the primary reference cited. The office action characterizes Dellinger as 1) not teaching the use of non-carbonate protecting groups, 2) not teaching the deprotection/oxidation step in non-aqueous solutions; and 3) not teaching a composition comprising an acid for removal of the non-carbonate protecting groups. Crameri is apparently cited as showing use of non-carbonate protecting groups, including acid-labile groups, in oligonucleotide synthesis. Manoharan likewise is apparently cited as showing use of non-carbonate protecting groups in oligonucleotide synthesis, including under substantially anhydrous conditions.

The office action then makes the unsupported statement that the deficiencies of Dellinger '030 “would have been obvious to the skilled artisan at the time of the invention when viewed in combination with Crameri and Manoharan.” The PTO has the burden of establishing a prima facie case of obviousness under 35 U.S.C. §103. It must show that some objective teaching in the prior art or knowledge generally held by one of ordinary skill would lead an individual to combine the relevant teachings of the references. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Therefore, a combination of relevant teachings alone is insufficient grounds to establish obviousness, absent some teaching or suggestion to do so. *Id.* at 1599. Combining references without sufficient suggestion of how to do so leads to error, and simply begs the question of how to arrive at the claimed method given the cited references.

Where the claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under 35 USC § 103 requires consideration of two factors: (1) whether the prior art would have suggested to one of

ordinary skill in the art to make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, one of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. In re Vaeck, 20 USPQ2d 1438, 1442 (CAFC 1991).

Applicants assert that substantial error was made in characterizing these references, and in combining the references, due to the difference in the chemistries used to accomplish the polynucleotide synthesis. Crameri makes clear (col. 16, lines 64-67; and col. 17, lines 9-23) that the method used therein for polynucleotide synthesis is based on the traditional three-step phosphoramidite process (skipping the coupling step). There is no showing or suggestion in Crameri to modify the methods to synthesize polynucleotides via a process having a concurrent oxidation/ deprotection step. Indeed, it is not even a focus of Crameri to teach or suggest novel chemistries for polynucleotide synthesis, since Crameri is directed to “family shuffling” of nucleic acids. Likewise, there is no showing or suggestion in Dellinger ‘030 to modify the carbonate protecting groups to those described as useful in the traditional phosphoramidite method used in Crameri.

The error in characterizing and combining the references becomes even more apparent with regard to the Manoharan patent. Manoharan does not show or even suggest that the compounds, protecting groups, and conditions used can be used in a polynucleotide synthesis scheme such as that shown in Dellinger ‘030 that proceeds via a phosphate intermediate and has a combined oxidation/ deprotection step.

In the patent of Manoharan the inventor is using the standard published H-phosphonate method of oligonucleotide synthesis (see Froehler and Matteucci, *Tetrahedron Lett.* **1986**, 27, 469-472) to produce chimerical oligonucleotides having linkages or pendent groups that may be degraded by repeated oxidation during the synthesis cycle. In the 2-step oligonucleotide synthesis described by Dellinger, the inventor is using the phosphite or phosphoramidite method of formation of internucleotide bonds. As originally described, the H-phosphonate method of

oligonucleotide synthesis produces an internucleotide H-phosphonate linkage that is more stable to acid and base treatment than the phosphite triester linkage produced by the phosphite or phosphoramidite method of oligonucleotide synthesis. This increased stability to acid and base allows for the oxidation step to be performed once at the end of the oligomerization process rather than repeatedly during the oligomerization process. In Manoharan the stated goal of this invention is to use this previously described method of post oligomerization oxidation along with various compositions and mixtures of known oxidants to limit or avoid degradation of linkages or pendent groups on chimerical oligonucleotides that could occur from repeated oxidation during the synthesis cycle. The oxidation of the internucleotide bond is still required as a separate step whether it occurs during the oligomerization process or post oligomerization. None of the methods utilized by Manoharan explicate or make obvious the simultaneous oxidation and deprotection required for 2-step oligonucleotide synthesis by the phosphite or phosphoramidite method. The acid or base deprotection conditions described by Manoharan are not applicable to phosphite or phosphoramidite oligonucleotide synthesis in absence of a separate oxidation step performed during oligomerization. In absence of this separate oxidation step the deprotection conditions described by Manoharan would result in degradation of the phosphite triester and not enable oligonucleotide synthesis. The deprotection conditions described by Manoharan can only be used in absence of oxidation with the H-phosphonate coupling method not the phosphite or phosphoramidite coupling methods. In the methods described by Manoharan the oxidation conditions are intended to oxidize the internucleotide bond and not perform additional reactions, especially reactions that would result in degradation of the modifications in his desired chimerical oligonucleotides. In the 2-step oligonucleotide synthesis described by Dellinger '030, the simultaneous oxidation and deprotection conditions are specifically designed to perform multiple specific reactions and enable a high yield, high integrity method of oligonucleotide synthesis.

There is no showing or suggestion in Manoharan to modify the methods to synthesize polynucleotides via a process having a concurrent oxidation/ deprotection step. There is no showing or suggestion in Manoharan to dispose of the H-phosphonate chemistry. Indeed, it is not even clear from the cited references how to combine the

multiple steps of the reactions described by each of the references to result in polynucleotide synthesis. Likewise, there is no showing or suggestion in Dellinger '030 to modify the carbonate protecting groups and/or reaction conditions to those described as useful for the H-phosphonate methods used by Manoharan. There is no credible showing of success or reasonable expectation of success by a skilled artisan on the date of the present invention, even if we were to assume that the particular elements from the prior cited prior art were reconstructed into a method according to the current claims. The discussion herein shows that the protecting groups and reaction conditions taught by the references exist within the context of the individual references, and cannot be separated out willy-nilly; therefore there is no reasonable expectation of success.

Even if a reader were to combine the cited references in such a way, picking and choosing some elements while purposefully omitting others from the combination to arrive at the method of the current claims, this still provides no more than a suggestion to try the combination. However, it is important to stress that obviousness is not established if a person of ordinary skill might find it obvious to try various combinations of the relevant teachings. "[T]his is not the standard of 35 U.S.C. §103." *In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

The current specification is the only source of teaching on the present record to combine the elements of the cited references (picking some elements, omitting others) to arrive at the claimed method. The applicants recognize that many of the features of their invention are disclosed in various ones of the references cited by or to the Patent Examiner. Nevertheless, none of the references teaches the unique combination of features called for in the claims. It is impermissible hindsight reasoning for the Examiner to pick a feature here and there from among the references to construct a hypothetical combination which obviates the claims. As stated in *In re Gorman*, 18 USPQ2d 1885 (Fed. Cir. 1991):

"It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps. [citation

omitted] The references themselves must provide some teaching whereby the applicant's combination would have been obvious.”

(Id. at 1888.) The test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention. See *In re Young*, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991).

As in the case of the cited art, a large number of methods may exist in the prior art where, if the prior art be disregarded as to its content, purpose, mode of operation and general context, the several elements claimed by the Applicants, if taken individually, may be disclosed. However, the important thing to recognize is that the reason for combining these elements in any way to meet applicants' claims only becomes obvious, if at all, when considered from hindsight in the light of the application disclosure. The Federal Circuit has stressed that the “decisionmaker must step backward in time and into the shoes worn by [a person having ordinary skill in the art] when the invention was unknown and just before it was made.” *Panduit Corp. v. Dennison Mfg. Co.*, 1 USPQ2d 1593, 1595-96 (Fed. Cir. 1987). To do otherwise would be to apply hindsight reconstruction, which is strongly discouraged by the Federal Circuit. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988); *In re Dow Chemical*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). Simply stating that the invention would have been obvious to a person of ordinary skill is also insufficient, for the assertion must be supported by clear and convincing evidence. *Panduit Corp. v. Dennison Mfg. Co.*, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987).

Therefore, without some reason or suggestion in the cited art to combine relevant prior art teachings, the Examiner has failed to establish a *prima facie* case for obviousness. The argument is sometimes made, citing *In re Sernaker*, 217 U.S.P.Q. 1 (Fed. Cir. 1983) and *In re Nilssen*, 7 U.S.P.Q.2d 1500 (Fed. Cir. 1988), that no express suggestion in the cited art for the combination is necessary. However, this begs the question. The issue is whether the references as a whole suggest the particular combination being used to obviate the claims. When the Examiner must resort to selecting elements of various teachings in order to form the claimed invention, he must establish first that there is a suggestion or motivation in the prior art to make the

particular selection made by the applicant. In re Gorman, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991), citing Interconnect Planning Corp. v. Feil, 227 USPQ 543, 551 (Fed. Cir. 1985). As stated in the Interconnect case:

“When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. [citation deleted] There must be ‘something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.’ [citation deleted].

* * *

“Not only must the claimed invention as a whole be evaluated, but so also must the references as a whole, so that their teachings are applied in the context of their significance to a technician at the time -- a technician without our knowledge of the solution.”

(Id.)

Thus the references should be taken as a whole, and as a whole fail to provide a reasonable expectation of success with the non-carbonate protecting groups, as claim 1 requires exposure “to a composition which concurrently oxidizes the phosphite formed in step (a) to a phosphate and deprotects the protected hydroxyl of the second nucleoside.” None of the cited references, alone or in combination, provide a reasonable expectation of success, when the full disclosure of each piece of cited art is considered as a whole (not just picking and choosing certain elements while eliminating others).

For the above reasons, the rejections of record are thought to be overcome, and the remaining claims allowable. Applicants request a timely Notice of Allowance for the remaining claims. If there are any unresolved issues that may be resolved via a phone call, the Examiner in charge of this case is invited to phone the undersigned attorney.

Respectfully submitted,
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